Docket No.: 10806-155

PATENT

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Linda G. Drake

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Appellant:	Barbro Hemmendorff et al	:	Paper No.:
Serial No.:	09/743,023	:	Group Art Unit: 1637
Filed:	March 7, 2001	:	Examiner: Chunduru, Suryaprabha

For: **METHOD FOR THE PRODUCTION OF RECOMBINANT PEPTIDES WITH A LOW AMOUNT OF TRISULFIDES**

REPLY BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The present Reply Brief is submitted in response to the Examiner's Answer mailed June 17, 2003.

I. SUMMARY

The Examiner's Answer maintains the rejection of claims 1-3, 5-8 and 11-22 under 35 U.S.C. §102(e) as being anticipated by Builder et al, U.S. Patent No. 5,663,304. The Examiner's Answer sets forth several incorrect assertions as well as raises at least four expanded points of argument with respect to this rejection. As set forth below, the expanded points of argument in the Examiner's Answer do not support the rejection of claims 1-3, 5-8 and 11-22 and, accordingly, Appellants respectfully request reversal of the rejection.

II. The Claimed Methods Are Not Inherent

At pages 5-7 of the Examiner's Answer, the Examiner expands the arguments relating to the Examiner's assertion that the claimed methods and the phrase "the low amount of trisulfides" are inherently disclosed by Builder et al. However, the present methods are not inherent in Builder et al and claims 1-3, 5-8 and 11-22 are not anticipated by and are patentably distinguishable from Builder et al. Accordingly, the rejection of the claims under 35 U.S.C. §102 should be reversed.

A. The Examiner's Position

The Examiner's Answer asserts that the claimed method and that of Builder et al result in the production of correctly folded recombinant polypeptides or proteins. The Examiner relies upon MPEP §2112.01 to state that, "products of identical chemical composition can not have mutually exclusive properties." The Examiner further asserts that a chemical composition and its properties are inseparable; therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present, citing *In re Spada*, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Examiner concludes that because both methods yield the same result (i.e., properly folded recombinant polypeptide), the reduction of trisulfides is inherent.

Additionally, the Examiner asserts that Builder et al disclose the addition of metal salt to the solvent medium explicitly to improve correct folding of the recombinant polypeptides. The Examiner also asserts that the inherency naturally flows from the disclosure of Builder et al because correct folding disulfide bonds (S-S bonds) and inhibition of intermediate aggregates of misfolded proteins is favored. The Examiner further asserts that the method as disclosed by Builder et al inherently teaches a reduction in the amounts of trisulfides because in the process of refolding of recombinant protein, free sulfhydryl groups and disulfides are

formed constantly, and to enhance the solubility of these intermediate conformations of protein, a suitable buffer is suggested by Builder et al.

B. Builder et al Does Not Anticipate Claims 1-3, 5-8 and 11-22

Appellants submit that not only do Builder et al fail to teach or recognize methods as defined by claims 1-3, 5-8 and 11-22, Builder et al do not inherently teach such methods, whereby the presently claimed methods are not anticipated by and are patentably distinguishable from Builder et al.

Appellants respectfully submit that the Examiner's reliance on MPEP §2112.01 is inapplicable to the examination of the present method claims. Specifically, the quotation applied by the Examiner is directed to inherency in composition claims and not method claims.

Moreover, Appellants respectfully submit that the Examiner's assertion that Builder et al disclose the addition of metal salt to the solvent medium explicitly to improve correct folding of the recombinant polypeptides is inaccurate. The Examiner sets forth several disclosures in Builder et al to support the Examiner's conclusion. However, these disclosures are directed to the addition of metal salt in a buffer during the refolding step, which is after peptide isolation. Appellants find no teaching or reference for adding a metal salt prior to peptide isolation for reducing trisulfide formation in the production of recombinant peptides. Builder et al only broadly assert that the fermentation medium may be "supplemented as necessary" with various components including, among others, salts (column 15, line 65--column 16, line 12). Accordingly, the present methods of adding a metal salt during or after the fermentation step, prior to peptide isolation, to reduce trisulfide formation is patentably distinguishable from adding a metal salt after peptide isolation to refold misfolded polypeptides, as disclosed by Builder et al.

The Examiner also asserts that Builder et al disclose the importance of adding metal salts in reducing protein aggregates or misfolded polypeptide aggregation. However, these disclosures are also directed to the addition of metal salt after peptide isolation. Specifically, Builder et al disclose at column 7, lines 10-28 the use of "copper or manganese salt to enhance refolding of misfolded polypeptides" and disclose at column 3, lines 1-22 the suitable buffers used during the refolding process. Each of these disclosures is directed to adding metal salts after peptide isolation to refold misfolded polypeptides, i.e., incorrect disulfide bonds have already been formed. In contrast, the present invention adds metal salts prior to peptide isolation to inhibit H_2S activity, thereby reducing trisulfide bond formation (see, for example, the specification at page 2, lines 20-30). Accordingly, Builder et al cannot inherently teach the present methods as Builder et al merely disclose adding metal salts after peptide isolation to refold misfolded polypeptides.

"In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art," *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat App & Int'f 1990). Inherency may not be established by "probabilities or possibilities," *Scaltech, Inc. v. Retec/Tetra, LLC.*, 51 USPQ2d 1055, 1059 (Fed. Cir. 1999). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient" to establish anticipation, *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981). In addition, to anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter, *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618 (Fed. Cir. 1996). The disclosure must be enabling to have placed it in the possession of a person of ordinary skill in the field of the invention, *In re Paulsen*, 31 USPQ2d 1671 (Fed. Cir. 1994).

In view of the failure of Builder et al to disclose methods for the production of recombinant peptides with a low amount of trisulfides, methods for the reduction of the amount of trisulfides in the production of recombination peptides or in the production of recombinant growth hormone, or methods for the reduction in the formation of the amount of trisulfides in the production of recombinant peptides as defined by the claims, wherein metal salt is added prior to peptide isolation, Builder et al do not disclose each element of the claims under consideration and do not enable one skilled in the art to produce the methods as recited by the claims. Therefore, Builder et al do not support a rejection of claims 1-3, 5-8 and 11-22 under 35 U.S.C. §102. The rejection should therefore be reversed.

III. The Preamble of the Claims Should Be Given Patentable Weight

At pages 7-8 of the Examiner's Answer, the Examiner expands the arguments that the preamble of the claims should not be given patentable weight. However, the preamble of a method claim must be given patentable weight, and, as a result, claims 1-3, 5-8 and 11-22 are not anticipated by and are patentably distinguishable from Builder et al. Accordingly, the rejection of the claims under 35 U.S.C. §102 should be reversed.

A. The Examiner's Position

In response to Appellants' position that the preamble of the claim should be given patentable weight, the Examiner asserts that in the instant invention, the limitation "low amount of trisulfides" in the preamble does not provide any significance to the claim construction because the claims are directed to the production of recombinant polypeptides, but not to the low amount of trisulfides or formation of reduced trisulfides. The Examiner also asserts that even if the preamble is given patentable weight, Builder et al inherently teach this limitation by adding metal salt to the process as discussed above.

The Examiner further asserts that Appellants argued that the actual values or concentration of the limitation "low amount of trisulfides" is not applicable to the instant claims 2 and 13-22, which clearly show that Appellants agree that the recitation of actual values or concentrations are required for claims 1, 3, 5-8 and 11-12. Therefore, the Examiner asserts that if the preamble should be given patentable weight, it should be recognized that the instant claims are more inclined to production of the low trisulfides or reduction of the amount of trisulfides, wherein the process steps do not recite how this limitation is achieved except for recitation of adding metal salts to the fermenting medium or after fermentation, which is recognized explicitly by Builder et al.

B. Builder et al Do Not Anticipate Claims 1-3, 5-8 and 11-22

Appellants submit that the preamble of the claims should be given patentably weight, whereby the methods as defined by claims 1-3, 5-8 and 11-22 are not anticipated by and are patentably distinguishable from Builder et al.

The Manual of Patent Examining Procedure §2111.02 states that "the claim preamble must be read in the context of the entire claim. The determination of whether preamble recitations are structural limitations or mere statements of purpose or use 'can be resolved only on review of the entirety of the [record] to gain an understanding of what the inventors actually invented and intended to encompass by the claims'. *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989)." Moreover, "preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise." *Boehringer Inselheim Vetmedica, Inc. v. Schering Plough Corp.*, 65 USPQ2d 1961, 1965 (CAFC 2003) citing *Griffin v. Bertina*, 62 USPQ2d 1431 (Fed. Cir. 2002). As disclosed in the specification and recited in the claims, the inventors

have invented methods for the production of recombinant peptides with a low amount of trisulfides, methods for the reduction of the amount of trisulfides in the production of recombinant peptides, and a method for the reduction in the formation of the amount of trisulfides in the production of recombinant peptides. Specifically, the present methods require the addition of metal salt prior to peptide isolation. The addition serves to inhibit H_2S activity, thereby reducing trisulfide bond formation (specification, page 2, lines 20-30). Therefore, gauging the effect of preamble language, it is apparent that the claim's preamble is part of the definition of the claimed subject matter and thereby, a limitation of the claim, see *Boehringer Inselheim Vetmedica, Inc., supra.*

The Examiner also asserts that Appellants argued that the actual values or concentration of the limitation "low amount of trisulfides" is not applicable to the instant claims 2 and 13-22, which clearly show that Appellants agree that the recitation of actual values or concentrations are required for claims 1, 3, 5-8 and 11-12. However, in Appellant's Appeal Brief, Appellants merely noted that the phrase "the low amount of trisulfides" is not recited in claims 2 and 13-22. With this notation, Appellants did not concede that the recitation of actual values or concentrations are required for claims 1, 3, 5-8 and 11-12. Appellants were merely clarifying to the Examiner that claims 2 and 13-22 recited different limitations than claims 1, 3, 5-8 and 11-12.

The Examiner further asserts that even if the preamble is given patentable weight the claims are inclined to production of low trisulfides or reduction of the amount of trisulfides, wherein the process steps do not recite how this limitation is achieved except for recitation of adding metals salts to the fermentation medium or after fermentation, which is recognized explicitly by Builder et al, see column 6, lines 52-60; column 7, lines 10-29; and column 12, lines 12-54. However, the disclosures, to which the Examiner relies, add metal salt to the

buffer during the refolding process, which occurs after peptide isolation. In contrast, the present invention requires that that the metal salt be added during or after fermentation, but prior to peptide isolation.

"Anticipation requires that every limitation of the claim in issue be disclosed, either expressly or under principles of inherency, in a single prior art reference," *Corning Glass Works v. Sumitomo Electric U.S.A. Inc.*, supra, at 1965 (Fed. Cir. 1989), *citing Kalman v. Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983), *cert. denied*, 224 USPQ 520 (1984). In view of the failure of Builder et al to disclose methods for the production of recombinant peptides with a low amount of trisulfides, methods for the reduction of the amount of trisulfides in the production of recombination peptides or in the production of recombinant growth hormone, or methods for the reduction in the formation of the amount of trisulfides in the production of recombinant peptides as defined by the claims, Builder et al do not disclose each element of the claims under consideration and therefore do not support a rejection of claims 1-3, 5-8 and 11-22 under 35 U.S.C. §102. The rejection should therefore be reversed.

IV. Builder et al Do Not Teach the pH Conditions as Recited in Claims 5 and 15

At page 8 of the Examiner's Answer, the Examiner expands the arguments relating to the patentability of claims 5 and 15. However, contrary to the expanded arguments, claims 5 and 15 are not anticipated by and are patentably distinguishable from Builder et al. Accordingly, the rejection of the claims under 35 U.S.C. §102 should be reversed.

A. The Examiner's Position

The Examiner asserts that Builder et al explicitly teach the pH conditions of claims 5 and 15 namely, "the pH is equal to or lower than pH 7."

B. Builder et al Do Not Anticipate Claims 5 and 15

Appellants submit that the Builder et al do not teach or recognize the pH conditions as defined by claims 5 and 15. Accordingly, Appellants submit that the methods as defined by claims 5 and 15 are not anticipated by and are patentably distinguishable from Builder et al.

Appellants respectfully submit that the Examiner's assertion that Builder et al disclose the pH conditions of claims 5 and 15 is inaccurate. The Examiner sets forth several disclosures of Builder et al to support the Examiner's conclusion. Specifically, the Examiner refers to the steps disclosed in Builder et al at column 16, lines 47-55 include steps which are after fermentation, but are during and after peptide isolation. In addition, the Examiner refers to the step of refolding the peptide, disclosed at column 28, lines 15-33 and column 31, lines 54-63, which is performed after the peptide is isolated by the precipitation step. These disclosures noted by the Examiner do not anticipate the limitations of claims 5 and 15 since the recited pH conditions of the claims are during or after fermentation, but prior to peptide isolation.

"Anticipation requires that every limitation of the claim at issue be disclosed, either expressly or under principles of inherency, in a single prior art reference," *Corning Glass Works, supra.* In view of the failure of Builder et al to disclose, either expressly or under principles of inherency, the methods pH conditions as recited in the claims 5 and 15, Builder et al do not disclose each element of the present claims and therefore do not anticipate claims 5 and 15 under 35 U.S.C. §102(e). The rejection should therefore be reversed.

V. Builder et al Do Not Teach the Production of Growth Hormone

At page 8-9 of the Examiner's Answer, the Examiner expands the arguments relating to the patentability of claims 8, 12, 18, 19 and 21. However, contrary to the expanded arguments, claims 8, 12, 18, 19 and 21 are not anticipated by and are patentably distinguishable from Builder et al. Accordingly, the rejection of these claims under 35 U.S.C. §102 should be reversed.

A. The Examiner's Position

The Examiner asserts that Builder et al disclose that the method is used to produce mammalian recombinant polypeptides such as growth hormone. Thus, the Examiner asserts that the method of Builder et al disclose the production of human growth hormone.

B. Builder et al Does Not Anticipate Claims 5 and 15

Appellants submit that the Builder et al do not teach, within the meaning of 35 U.S.C. §102, the production of recombinant growth hormone as defined by claims 8, 12, 18, 19 and 21. Accordingly, Appellants submit that the methods as defined by claims 8, 12, 18, 19 and 21 are not anticipated by and are patentably distinguishable from Builder et al.

Builder et al fail to provide a specific teaching in the examples of the production of a peptide, such as growth hormone, which involves trisulfide formation. Moreover, Insulin-Like Growth Factor (IGF-I), the peptide to which Builder et al specifically refer, and exemplify, is not known, as previously acknowledged by the Examiner, to produce trisulfides when the polypeptide is formed. Accordingly, Builder et al do not teach or enable the methods as defined by the claims under 35 U.S.C. §102.